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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Congress of Neurological Surgeons systematic review and evidence-based guideline for the management of patients with residual or recurrent nonfunctioning pituitary adenomas.

Bibliographic Source(s)

Sheehan J, Lee CC, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Zada G, Aghi MK. Congress of Neurological Surgeons systematic review and evidence-based guideline for the management of patients with residual or recurrent nonfunctioning pituitary adenomas. Neurosurgery. 2016 Oct;79(4):E539-40. PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Question

Should patients with recurrent or residual nonfunctioning pituitary adenomas (NFPAs) undergo stereotactic radiosurgery (SRS), fractionated radiation therapy (e.g., fractionated radiotherapy [XRT], fractionated stereotactic radiotherapy [SRT], or intensity modulated radiotherapy [IMRT]), or repeat resection?

Target Population

These recommendations apply to adult patients with recurrent or residual NFPAs.

Level II Recommendations

- Radiosurgery and radiation therapy are recommended for treatment of residual or recurrent NFPAs to lower the risk of subsequent tumor progression.
- When no residual tumor is present or only a small intrasellar tumor exists postoperatively, serial neuroimaging studies are recommended.
- Radiosurgery using single-session doses of 12 or more Gy or radiation therapy with fractionated doses of 45 to 54 Gy is recommended for greater local tumor control rate of 90% or higher at 5 years after treatment.

Level III Recommendations

- Assessment of NFPA proliferative index and adrenocorticotrophic hormone (ACTH) staining to identify silent corticotrophic adenomas are recommended for providing guidance regarding the risk of adenoma progression and the benefit of earlier adjuvant radiation.
- Repeat resection is recommended for the treatment of symptomatic recurrent or residual NFPAs.
- Radiosurgery or radiation therapy for NFPAs is recommended when residual/recurrent sellar or parasellar tumor exists and the risk of a repeat resection is high.

Definitions

Evidence Classification for Therapeutic Studies

Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls

Strength of Recommendations Rating Scheme

Level I: High degree of clinical certainty (Class I evidence or overwhelming Class II evidence)

Level II: Clinical certainty (Class II evidence or a strong consensus of Class III evidence)

Level III: Clinical uncertainty (inconclusive or conflicting evidence or opinion)

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Residual or recurrent nonfunctioning pituitary adenoma (NFPA)

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Endocrinology

Neurological Surgery

Neurology

Oncology

Radiation Oncology

Radiology

Intended Users

Physicians

Guideline Objective(s)

- To critically evaluate the evidence to support the options of repeat microsurgical resection, stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT), and fractionated radiation therapy (XRT)
- To provide guidelines for the use of the approaches in the management of recurrent or residual nonfunctioning pituitary adenomas (NFPAs)

Target Population

Adult patients with residual or recurrent nonfunctioning pituitary adenomas (NFPA)

Interventions and Practices Considered

1. Stereotactic radiosurgery (SRS)
2. Fractionated radiation therapy (XRT)
3. Stereotactic radiation therapy (SRT)
4. Serial neuroimaging
5. Assessment of nonfunctioning pituitary adenoma (NFPA) proliferative index and adrenocorticotrophic hormone (ACTH)
6. Repeat resection

Major Outcomes Considered

- Tumor recurrence rate
- Gross total resection rate
- Tumor control rate
- Complication rate
- Perioperative mortality
- Progression-free survival

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Search Strategy

Literature Search

The guideline task force collaborated with a medical librarian to search for articles published from January 1, 1966, to October 1, 2014. Searches were conducted in two electronic databases, PubMed and The Cochrane Central Register of Controlled Trials. Strategies for searching electronic databases were constructed by the guideline task force members and medical/research librarians using previously published search strategies to identify relevant studies. The root search strategies are provided in Appendix A of the introduction and methodology companion and the chapter-specific search strategies are provided in the appendix of the full version of the guideline (see the "Availability of Companion Documents" field).

The searches of electronic databases were supplemented with manual screening of the bibliographies of all retrieved publications. The bibliographies of recent systematic reviews and other review articles for potentially relevant citations were also screened. All articles identified were subject to the study selection criteria listed below. The guideline task force also examines lists of included and excluded studies for errors and omissions.

Article Inclusion Criteria

Articles were retrieved and included only if they met specific inclusion criteria. These criteria were also applied to articles provided by the evidence-based clinical practice guideline task force members who supplemented the electronic database searches with manual searches of the bibliographies. To reduce bias, these criteria were specified *a priori* before conducting the literature searches. For the purposes of this guideline, articles had to meet the following criteria to be included as evidence to support the recommendations presented in this guideline:

- Investigated patients suspected of having a pituitary mass
- Enrolled patients ≥18 years of age
- Either enrolled exclusively nonfunctioning pituitary adenoma (NFPA) patients OR combined the results of patients with NFPAs and functioning pituitary adenomas and/or other pituitary masses with ≥90% of the patients having NFPAs
- Was a full article report of a clinical study
- If a prospective case series, reported baseline values
- Appeared in a peer-reviewed publication
- Enrolled ≥10 NFPA patients per arm per intervention (20 total) for each outcome
- Was of humans
- Was published in or after 1966
- Quantitatively presented results

Article Exclusion Criteria

Articles of the following types were excluded as evidence to support the recommendations presented in this guideline:

- In vitro studies
- Studies performed on cadavers
- Studies not published in English
- Medical records reviews, meeting abstracts, historical articles, editorial, letters, or commentaries
- Systematic reviews, meta-analyses, or guidelines developed by others

Specific Methods for This Guideline

Literature Search

The task force collaborated with a medical librarian to search for articles published from January 1, 1966, to October 1, 2014. Authors searched 2 electronic databases, PubMed and The Cochrane Central Register of Controlled Trials. Strategies for searching electronic databases were constructed by the evidence-based clinical practice guideline taskforce members and the medical librarian, using previously published search strategies to identify relevant studies (see Appendix A in the full guideline). The Cochrane Library was searched for all NFPA articles. There were no specific Cochrane reviews for pituitary adenomas. Therefore, all appropriate references were found in the PubMed search.

Results

The search resulted in 95 articles, and 46 were excluded based on the inclusion and exclusion criteria mentioned above according to the title and abstract.

Number of Source Documents

The remaining 49 articles were included and these were as follows: outcome of repeat surgical resection (n = 4), outcome of radiosurgery (i.e., single-session or hypofractionated stereotactic radiosurgery [SRS]) (n = 24), or fractionated radiotherapy (i.e., stereotactic radiotherapy [SRT], conventional fractionated radiotherapy [XRT]) (n = 21).

A flow diagram of the search process summarizing study selection can be found in Figure 1 in the full version of the guideline (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification for Therapeutic Studies

Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Statistical Analyses of Pooled Data

To compare the tumor control rates between patients who underwent adjuvant radiation therapy and patients who were treated conservatively, the pooled data were analyzed using Review Manager version 5.2.8. The tumor control rates were extracted for the patients who underwent stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT), and fractionated radiation therapy (XRT) as adjuvant treatment, and for patients who chose observation. Studies with tumor control rates of nonfunctioning adenoma (NFA) comparing adjuvant SRS and observation were included in the meta-analysis. Odds ratios for individual studies and the sum of the included studies were computed using the Mantel-Haenszel test.

Under the assumptions of possible clinical diversity among the included studies, the random effects model was implemented in the analyses for this review. Study heterogeneity was detected using the chi-square and I^2 test statistics. In general, a small number of studies in the analyses lower the power of the chi-square test. Therefore, both a chi-square value within the 10% (P <.10) and an I^2 value exceeding 50% were required for significance.

The result of the meta-analysis is demonstrated in Figure 2 in the full version of the guideline (see the "Availability of Companion Documents" field).

Rating the Quality of the Evidence and Levels of Recommendations

The quality and classification of evidence (see the "Rating Scheme for the Strength of the Evidence" field) was rated using an evidence hierarchy developed by the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Guidelines Committee for each of four different study types: therapeutic, prognostic, diagnostic, and economic or decision modeling. The methodology used to conduct quality evaluations of the evidence can be located on the CNS Web site (see also the "Availability of Companion Documents" field). The level/strength of recommendation (i.e., Level I, II, or III) was linked to the quality of the overall body of evidence included in the chapter and in support of a given recommendation.

Methods Used to Formulate the Recommendations

Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

Process Overview

A multidisciplinary task force comprised of physician volunteers and evidence-based medicine trained methodologists conducted a systematic review of the literature relevant to the management of non-functioning pituitary adenomas (NFPAs). The physician volunteers represented neurosurgeons, neuro-ophthalmologists, neuroradiologists, and endocrinologists with expertise in pituitary adenomas. The evidence-based medicine trained methodologists had previous experience in guidelines production for the Joint Guidelines Committee (JGC) of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS). During the development process, the task force participated in a series of conference calls and meetings. Multiple iterations of written review were conducted by the individuals of the panel and various CNS/AANS Committees prior to approval.

Guideline Task Force Panel Consensus

The guideline task force panel included context experts from multiple disciplines and various areas of therapy to address the topics addressed in this guideline. Sub-task force members were assigned to a specific chapter and were involved in the literature review, the creation and editing of the evidence tables, reviewing and voting of the final recommendations.

Voting on the Recommendations

The task force used a structured voting technique to finalize and approve the final recommendations, language, and strength of recommendations, presented in this review. The voting technique is referred to as the nominal group technique. This technique includes up to three rounds of voting, using secret ballots to ensure task force members are blinded to the responses of other task force members. All the recommendations in this review were approved following the first round of voting and no further discussion was needed to finalize the recommendations. During the course of editing and finalization of the document, changes were made to allow recommendations to conform to the rules of evidence and language as described above. When this occurred, the changes were reviewed and approved by the group.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations Rating Scheme

Level I: High degree of clinical certainty (Class I evidence or overwhelming Class II evidence)

Level II: Clinical certainty (Class II evidence or a strong consensus of Class III evidence)

Level III: Clinical uncertainty (inconclusive or conflicting evidence or opinion)

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Approval Process

The guideline draft was circulated to the entire task force for final review and approval prior to submission for peer review by the Joint Guidelines Committee (JGC) of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS). Due to the reviewers' knowledge of evidence-based medicine and clinical practice guidelines methodology training, the JGC peer reviewers served as the journal's editorial reviewers. As a part of the JGC review process, the reviewers provided input on the content of the guideline and suggested revisions prior to approval and endorsement of the draft guideline by the CNS and AANS prior to publication. The development of this guideline was editorially independent from the funding agencies (CNS Executive Committee, and AANS/CNS Joint Tumor Section Executive Committee), the CNS and Joint Tumor Section.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

No class I evidence was available; 6 studies met criteria for class II evidence; and other studies provided class III evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

For patients with residual or recurrent NFPA, long-term tumor control can be achieved with radiation. For those with a known residual adenoma, radiographic signs of progression make for a more compelling reason to intercede and retreat the adenoma. Radiographic signs of progression in the setting of younger patients or patients with symptoms attributable to progression should be considered even more strongly for intervention.

Potential Harms

- Repeat Resection: Although there is no direct comparison, second transsphenoidal approaches appear to convey higher complication rates, varying from 1% to 22%. The complications include hypopituitarism (<5%), cerebrospinal fluid (CSF) leakage (1.5%-2.5%), postoperative hyponatremia (3.7%), transient or permanent diabetes insipidus (<5%), visual deterioration (<5%), meningitis (2.5%), hematoma on the tumor bed (1.7%), epistaxis, sinusitis, and anesthetic risks. Incomplete resection or failure to identify the remaining adenoma secondary to obscured anatomy can also occur during repeat resection.
- Stereotactic Radiosurgery (SRS): Hypopituitarism is the most frequently occurring unintended side effect of radiosurgery. Rates of hypopituitarism ranged from 0% to 39% in the identified series. The second most common side effect from radiosurgery is a cranial neuropathy. Optic nerve dysfunction varied from 0% to 12.8%. Other deficits involving cranial nerves III, IV, and VI varied from 0% to 13.7%.
- Fractionated Radiation Therapy: Immediate side effects may include nausea and some fatigue. These symptoms are usually mild, but they may last 1 to 2 months after radiation treatment. Hair loss at the entry sites, decreased taste, and diminished olfaction can also occur. Similar to SRS, the most common side effect is radiation-induced hypopituitarism. Hypopituitarism in the studies that met inclusion criteria ranged from 0% to 88%. Using conventional dose and fractionation schemes, the rate of radiation-induced damage to the visual pathways is 1% to 5%. Rare instances of radiation-induced tumor formation (e.g., parasellar fibrosarcomas), cerebral ischemia from carotid stenosis, and neuropsychological or cognitive changes have also been described. Cerebrovascular complications following radiation therapy were noted to be 4.5% in one series. In another series of 120 patients previously noted, radiation-induced neoplasia occurred in 1.7% of patients.

Qualifying Statements

Qualifying Statements

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. The presentations are designed to provide an accurate review of the subject matter covered. This guideline is disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in its development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a physician should be sought. The recommendations contained in this guideline may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guideline must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Sheehan J, Lee CC, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Zada G, Aghi MK. Congress of Neurological Surgeons systematic review and evidence-based guideline for the management of patients with residual or recurrent nonfunctioning pituitary adenomas. Neurosurgery. 2016 Oct;79(4):E539-40. PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Oct

Guideline Developer(s)

Congress of Neurological Surgeons - Professional Association

Source(s) of Funding

These evidence-based clinical practice guidelines were funded exclusively by the Congress of Neurological Surgeons and the Tumor Section of the Congress of Neurological Surgeons and the American Association of Neurological Surgeons, which received no funding from outside commercial sources to support the development of this document.

Guideline Committee

Nonfunctioning Pituitary Adenoma Guideline Task Force

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Potential Conflicts of Interest

All Nonfunctioning Pituitary Adenoma (NFPA) Guideline Task Force members were required to disclose all potential conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Joint Guidelines Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and restrict the writing, reviewing and/or voting privileges of that person to topics that are unrelated to the possible COIs.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Guideline Endorser(s)

American Association of Neurological Surgeons - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Neurosurgery Web site . Also available in ePub format from the Neurosurgery Web site .

Availability of Companion Documents

The following are available:

- Sheehan J, Lee CC, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Zada G, Aghi MK. Congress of Neurological Surgeons systematic review and evidence-based guideline for the management of patients with residual or recurrent nonfunctioning pituitary adenomas. Full guideline. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2016 Oct. 28 p. Available from the Congress of Neurological Surgeons (CNS) Web site .
- Aghi MK, Chen CC, Fleseriu M, Newman SA, Lucas JW, Kuo JS, Barkhoudarian G, Farrell CJ, Sheehan J, Ziu M, Dunn IF. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the management of patients with nonfunctioning pituitary adenomas: executive summary. Neurosurgery. 2016 Oct;79(4):521-3. Available from the Neurosurgery Web site .
- Aghi MK, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Zada G. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the management of patients with nonfunctioning pituitary adenomas: introduction and methodology. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2016 Oct. 12 p. Available from the CNS Web site .
- Congress of Neurological Surgeons (CNS). Guideline development methodology: endorsed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Guideline Committee. Schaumburg (IL): Congress of Neurological Surgeons (CNS); 2012 Feb. 12 p. Available from the CNS Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 10, 2017. The information was verified by the guideline developer on February 22, 2017.

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